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10/596,169	06/02/2006	Brian MacDonald	PB60601	3131

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EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/596,169	MACDONALD, BRIAN	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-28 are pending. Claims 29-45 have been cancelled.

Comment: In claim 20, "does not also suffers" reads awkwardly and the Examiner requests correction.

Drawings

The drawings are objected to because: 1) Figures 1 and 2 are too unclear to view the details in the graphs; and 2) Figures 3-9 are either too dark or out of focus to convey any useful information. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Determination of Claim Scope

Claims 1, 10 and 21 of the instant application claim a pharmaceutical composition comprising rosiglitazone or a pharmaceutically acceptable salt or ***solvate*** thereof.

Review of Applicants' Disclosure

The instant specification does not disclose, to which solvates of rosiglitazone Applicants are referring. Applicants' specification does not disclose how to make any particular solvate nor do Applicants depict chemical structures of rosiglitazone as any particular solvate in their disclosure.

Possession Based Ordinary Skilled Artisan's Determination/ State of the Prior Art

It is generally accepted in the art that the formation of a particular solvate or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 18), therefore, the generic reference to a solvate of rosiglitazone in the instant specification does not provide adequate written support for claims drawn to any solvate of this compound. An ordinary skilled artisan would conclude that Applicants were not in possession of any particular solvate of rosiglitazone. Furthermore, because Applicants' generic reference to solvates of rosiglitazone does not permit the ordinary skilled artisan to clearly envisage what specific any one or more solvates were in Applicants' possession, the only reasonable conclusion said artisan would make was that Applicants were not in possession of solvates of rosiglitazone and had not reduced to practice the preparation, isolation, and characterization of said solvates.

The remaining claims are rejected as depending from a rejected claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutically acceptable salts of rosiglitazone, does not reasonably provide enablement for compositions comprising solvates of

rosiglitazone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicant's claims are broad with regards to the subgenera of solvates of rosiglitazone.

Nature of the invention

Claims 1, 10 and 21 of the instant application are drawn to methods of treating psoriasis comprising administering to a patient in need thereof by the oral route a pharmaceutical

composition comprising rosiglitazone or a pharmaceutically acceptable salt or solvate thereof and kits for the treatment of psoriasis are representative of the nature of Applicants' invention.

State of the Prior Art

It is generally accepted in the art that the formation of a particular solvate or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 11 and 15-18). Ellis et al. (Archive Dermatol 2000, 136, 609-616) report that oral troglitazone improved psoriasis in all patients and that PPAR γ ligands for PPAR γ may be of clinical value in the treatment of psoriasis (Abstract and page 615, left column).

Level of One of Ordinary Skill

The level of a person of ordinary skill in the art of pharmaceutical/medical research is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof).

Predictability/Unpredictability in the Art

There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970). The art is especially unpredictable with regards to the existence and formation of particular polymorphs and pseudopolymorphs (e.g. hydrates and solvates) of chemical compounds, as set forth above by the teachings of Vippagunta et al. Furthermore, Vippagunta et al. teach that phase transitions such as desolvation of solvate can alter the dissolution rate and transport characteristics of the drug which in turn would effect the

boiavailability of the drug (Abstract and page 17, 3.3 Phase transformation of hydrates and solvates).

Furthermore with respect to the compounds used to treat psoriasis, on the one hand Kurtz (US 5,594,015) discloses methods and compositions of thiazolidine derivatives for the treatment of psoriasis (Abstract and claims 1-23). In addition, Ellis et al. (Archive Dermatol 2000, 136, 609-616) report that oral troglitazone improved psoriasis in all patients and that PPAR γ ligands for PPAR γ may be of clinical value in the treatment of psoriasis (Abstract and page 615, left column). However on the other hand, the art teaches that twice daily topical administration of 0.5% rosiglitazone (a thiazolidinedione) to plaque psoriasis over a 30 day period did not exert a strong antipsoriatic effect (Abstract: Kuenzli et al. Dermatology 2003, 206(3), 252-256). Therefore, it is unpredictable in the art as to which thiazolidine derivatives are effective for the treatment of psoriasis.

Guidance/Working Examples

Applicants provide no guidance or working examples about the preparation of any solvates of rosiglitazone.

The quantity of experimentation necessary

It would require an undue amount of experimentation to determine: 1) which solvates of rosiglitazone can be made and 2) which solvates might work in the invention because it is clear from Vippagunta et al. that changes in solvation have direct consequences for bioavailability. This is further compounded by the fact that the art teaches away from treating psoriasis with rosiglitazone because topical administration of rosiglitazone to plaque psoriasis has no effect (see

above). In conclusion, the specification, while being enabling for compositions comprising pharmaceutically acceptable salts of rosiglitazone, does not reasonably provide enablement for compositions comprising solvates of rosiglitazone.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-6, 20-22 and 28 are rejected under 35 U.S.C. 102(a) as being anticipated by Needleman (US 2003/0220374).

Needleman discloses methods and kits for the treatment of inflammation related disorders such as psoriasis with peroxisome proliferator activated receptor agonist (Abstract; claims 1-33, 38-51, 53, 54 and 56). The method comprises administering enterally, which encompasses oral administration, in one or more doses per day (claim 30) an amount of PPAR receptor agonist with a range of from about 0.01 to about 20 mg/day per kg of body weight (claim 17) wherein the disorder can be psoriasis (claim 22). Needleman thus anticipates the instant methods and kit claims. Consequently, it is the Examiner's position that instant claims 1-6, 20-22 and 28 are fairly disclosed by Needleman. With respect to the kit instructions: Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art." *In re Ngai*, >367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004).

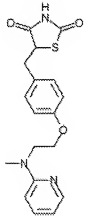
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 16 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Rivier et al. (US 6,403,656).

Rivier et al. disclose methods of treating skin disorders such as psoriasis comprising administering an effective amount of 5-{4-[2-methyl-pyrid-2-ylamino)ethoxy]benzyl}thiazolidine-2,4-dione (rosiglitazone) (claim 1). Please note the IUPAC chemical name.



Rosiglitazone

Systematic (IUPAC) name
5-((4-(2-(methyl-2-pyridinylamino) ethoxy)phenyl) methyl)- 2,4-thiazolidinedione

Rivier et al. disclose that administration can be enteral, which reads on oral, and in the form of tablets, capsules, dragees, syrups, powders and suspensions and which anticipate the oral

route (column 2, lines 59-67). The compounds are administered at a daily dose of 0.001 mg/kg to 100 mg/kg of body weight taken in 1 to 3 doses which anticipates the instant 2, 4 and 8 mg of rosiglitazone per day (column 3, lines 5-8). Patients suffering from moderate or severe psoriasis are inherent in the method of treating psoriasis. In the absence of evidence to the contrary the patients do not have non-insulin dependent diabetes mellitus. Therefore, the Examiner concludes that Rivier et al. fairly disclose the methods of instant claims 1-6 and 20.

Rivier et al. disclose using other anti-psoriatic drugs, thus reading on instant claim 16 (column 3, lines 33-34) as well as inert and active ingredients (column 3, lines 22-48). In one embodiment, Rivier et al. disclose a package (column 2, lines 60-63).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rivier et al. (US 6,403,656) in view of Cutie et al. (US 6,468,507) and Shroot (US 4,405,615) and Needleman (US 2003/0220374).

Please note that with respect to the 112 first paragraph rejections above, this rejection is over the subject matter that has written description and enablement.

Applicant claims methods of treating psoriasis comprising administering to a patient in need thereof by the oral route a pharmaceutical composition comprising rosiglitazone or a pharmaceutically acceptable salt thereof and kits for the treatment of psoriasis

Determination of the scope and content of the prior art

(MPEP 2141.01)

The reference of Rivier et al. is discussed in detail above and that discussion is hereby incorporated by reference. The reference of Needleman is discussed in detail above and that discussion is hereby incorporated by reference.

Cutie et al. teach methods of treating in a human by oral inhalation of 1 to 500 mg rosiglitazone maleate (claims 1, 11 and 12). Cutie et al. teach combining a hormone with the rosiglitazone maleate (claim 2).

Shroot et al. teach methods of treating psoriasis with hydrocortisone (claims 1 and 11).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Rivier et al. is that Rivier et al. do not expressly teach diagnosing moderate, severe or very severe psoriasis in a patient as well as whether or not the patient suffers from non-insulin dependent diabetes mellitus and continued treatment for 12 weeks or more or 18 weeks or more.

2. The difference between the instant application and Rivier et al. is that Rivier et al. do not expressly teach the maleate salt of rosiglitazone. This deficiency in Rivier et al. is cured by the teachings of Cutie et al.

3. The difference between the instant application and Rivier et al. is that Rivier et al. do not expressly teach adding hydrocortisone to the treatment/kit with a fast onset of activity. This deficiency in Rivier et al. is cured by the teachings of Shroot.

4. The difference between the instant application and Rivier et al. is that Rivier et al. do not expressly teach a kit with instructions for the oral administration of 2 to 8 mg of rosiglitazone. This deficiency in Rivier et al. is cured by the teachings of Needleman and Cutie et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to diagnose moderate, severe or very severe psoriasis in a patient as well as whether or not the patient suffers from non-insulin dependent diabetes mellitus and continued treatment for 12 weeks or more or 18 weeks or more, in the method of Rivier et al. and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because the patient has to have psoriasis and it is merely subjective to label the severity of the psoriasis. With respect to the duration of treatment, it is merely routine optimization to determine how long treatment should last. Clearly the period of treatment is a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal duration of treatment needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of treatment duration would have been obvious at the time of applicant's invention. With respect to the non-insulin dependent diabetes mellitus limitation, it is deemed irrelevant whether or not the patient suffers from this or not because the treatment is directed to psoriasis and not diabetes mellitus. This point of view is supported by claims directed to patients without diabetes mellitus (see claim 20).

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the maleate salt of rosiglitazone in the method of Rivier et al., as suggested by Cutie et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Cutie et al. teach that the maleate salt dissolves rapidly in the epithelial lining fluids and is absorbed quickly across the biomembranes of the patient which would have motivated one of ordinary skill in the art to select this rosiglitazone salt over any other salt because of the enhanced bioavailablity (column 2, lines 25-31).

3. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to add hydrocortisone to the method of Rivier et al., as suggested by Shroot, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

4. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a kit out of the composition of Rivier et al., as suggested by Needleman, using the maleate salt of rosiglitazone, as suggested by Cutie et al, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because kits comprising PPAR receptor agonists are taught in the art as evidenced by Needleman. Addition of hydrocortisone to the kit for the same purpose is obvious as evidenced by Shroot. The benefits of using the maleate salt are discussed above. With respect to administering the hydrocortisone until the rosiglitazone becomes effective is merely routine optimization of the treatment. With respect to the limitations of the patient suffering or not from diabetes mellitus, please see the discussion above. The details of the instructions are, in this case, irrelevant. Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related

to the product, the content of the printed matter will not distinguish the claimed product from the prior art." *In re Ngai*, >367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/
Examiner, Art Unit 1616